REMARKS

Reconsideration of the present application, as amended, is respectfully requested.

Since the present amendment raises no new issues for consideration and, in any event, places the present application in better condition for consideration on appeal, it is respectfully requested that this amendment be entered under 37 CFR 1.116 in response to the last Office Action dated May 30, 2003, which made final rejections as to the pending claims.

A. STATUS OF THE CLAIMS

As a result of the present amendment, claims 1-8, 10-16 and 18-37 remain in the case for continued prosecution.

B. REJECTIONS UNDER 35 U.S.C. § 112, 2nd PARAGRAPH

At page two, paragraph 2, of the office action, the Examiner has objected to claims 1-16, 18-30 and 32-37 under 35 U.S.C. § 112, 2nd paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants have amended the last two lines of claim 1 to insert "target cell" before 'and". Applicants have also deleted the limitation of $Z[D]_y$ from the last two lines of both claims 36 and 37. The dependency of claim 18 has been changed from 17 (cancelled) to claim 2. Claim 32 has been amended to indicate that Z becomes covalently linked after the reaction. Claim 37 has been amended to clarify that L_1 is the bifunctional group. In view of the amendments to the claims, it is urged that the rejections under 35 U.S.C. § 112, 2nd paragraph have been overcome.

C. OBJECTIONS IN THE CLAIMS

At page 2, paragraph 3 of the office action, the Examiner has objected to various informalities in the claims. Applicants have amended the claims to correct these informalities.

At page 3, paragraph 4 of the office action, the Examiner has stated that claims 9 and 36 are identical in scope. Applicants have, therefore, canceled claim 9. Additionally, Applicants confirm that claims 14 and 37 are not identical in scope.

In view of the amendments to and cancellation of the claims, it is urged that the objections

cited herein by the Examiner have been overcome.

D. ALLOWABLE SUBJECT MATTER

At page 3, paragraph 6 of the office action, the Examiner has indicated that claim 31 is allowed and that claims 1-16, 18-30 and 32-37 would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. § 112, 2nd paragraph. Applicants have amended the claims and it is urged that the rejections/objections cited herein by the Examiner have been overcome.

E. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that this Amendment is being facsimile transmitted to the Commissioner for Patents on the date shown below.

MUSERLIAN, LUCAS & MERCANTI, LLP

BY: _____
Michael N. Mercanti

AMENDMENT UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP ART UNIT 1654

Docket No. 213.1079-CIP3

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: RUSSEL, J.E. Art Unit: 1654

Re: Application of: Greenwald, et al.

Serial No.: 09/758,993

Filed: January 12, 2001

For: **TETRAPARTATE PRODRUGS**

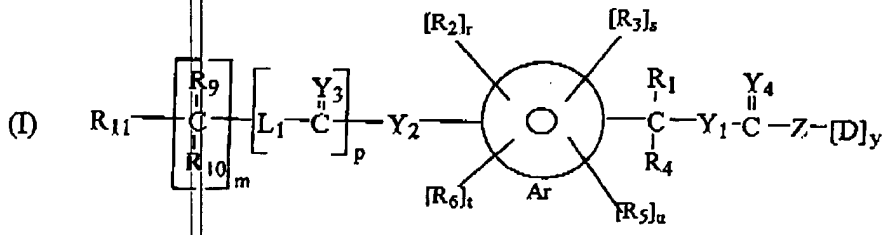
APPENDIX - Version Showing Changes Made

IN THE CLAIMS:

Please cancel claim 9.

Please amend claim 1 as follows:

1. (Twice Amended) A compound of Formula I:



wherein:

L_1 is a bifunctional linking moiety;

D is a moiety that is a leaving group, or a residue of a compound to be delivered into a cell;

Z is covalently linked to $[D]_y$, wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

Y_1, Y_2, Y_3 and Y_4 are each independently O, S, or NR_{12};

R_{11} is a mono- or divalent polymer residue;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkylcarbonyls;

Ar is a moiety which when included in Formula (I) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

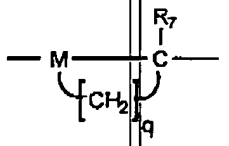
(m), (r), (s), (t), and (u) are independently zero or one;

(p) is zero or a positive integer; and (y) is 1 or 2;

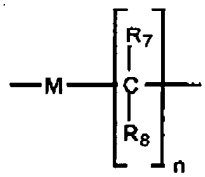
wherein $Z[D]_y$ is capable of crossing the membrane of the target cell and is capable of being hydrolyzed therein to release D.

Please amend claim 2 as follows:

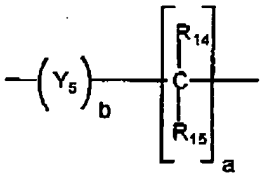
2. (Amended) The compound of claim 1, wherein L_1 is selected from the group consisting of:



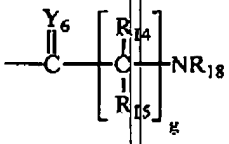
,



,



, and



wherein:

M is X or Q; where X is an electron withdrawing group;

Q is a moiety containing a free electron pair positioned three to six atoms from $-\overset{\overset{Y_3}{\|}}{C}-$;

(a) and (n) are independently zero or a positive integer;

(b) is zero or one;

(g) is a positive integer;

(q) is three or four;

R_7, R_8, R_{14}, R_{15} and R_{18} are independently selected from the group which defines R_9; and

Y_5 and Y_6 are independently O, S, or NR_{12}.

Please amend claim 7 as follows:

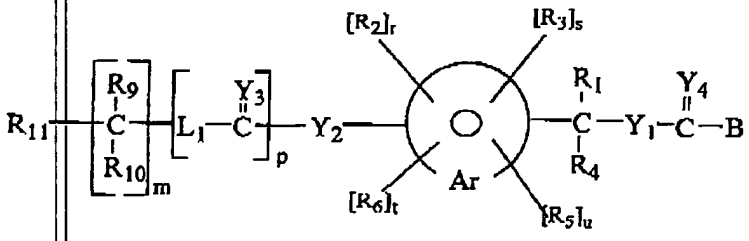
7. (Twice Amended) The compound of claim 6 wherein the peptide is Gly-Phe-Leu-Gly (SEQ ID NO:1) or ~~(SEQ ID NO:1)~~ Gly-Phe-Leu.

Please amend claim 18 as follows:

18. (Amended) The compound of claim ~~17~~ 2, wherein X is selected from the group consisting of O and NR_{12}.

Please amend claim 31 as follows:

31. (Twice Amended) A method of preparing a tetrapartate prodrug comprising reacting a compound of formula:

III 

with a compound of formula:

IV $\quad Lx - Z - [D]_y;$

wherein B is a leaving group for Formula III~~a~~;

L_1 is a bifunctional linking moiety;

D is a moiety that is a leaving group, or a residue of a compound to be delivered into a cell;

Lx is a leaving group for Formula IV;

Z is covalently linked to $[D]_y$, wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkylcarbonyls;

Ar is a moiety which when included in Formula (III) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

(m), (r), (s), (t), and (u) are independently zero or one;

(p) is zero or a positive integer;

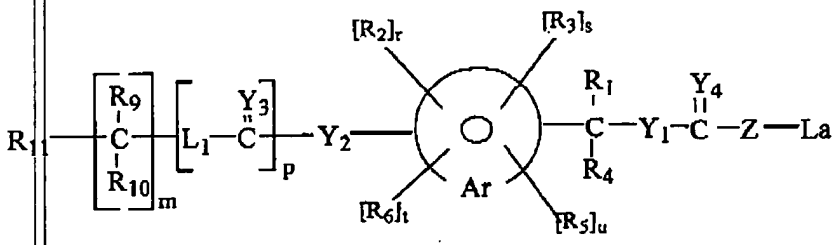
(y) is one or two;

Y_1, Y_2, Y_3 and Y_4 are each independently O, S, or NR_{12} ; and

R_{11} is a monovalent or divalent polymer residue.

Please amend claim 32 as follows:

32. (Twice Amended) A method of preparing a tetrapartate prodrug comprising reacting a compound of formula

V 

with at least one biologically active material; wherein

L_1 is a bifunctional linking moiety;

La is a leaving group for Formula V;

Z is covalently linked to La and wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkylcarbonyls;

Ar is a moiety which when included in Formula (V) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;
(m), (r), (s), (t), and (u) are independently zero or one;

(p) is zero or a positive integer;

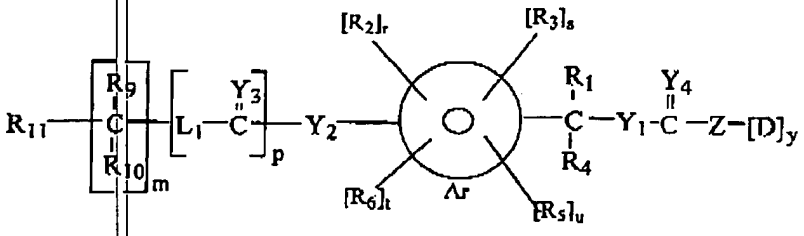
Y_1, Y_2, Y_3 and Y_4 are independently O, S, or NR_{12} ; and

R_{11} is a monovalent or divalent polymer residue

wherein after the reaction Z is covalently linked to the at least one biologically active material.

Please amend claim 36 as follows:

36. (Amended) A compound of Formula I:

(I) 

wherein:

L_1 is a bifunctional linking moiety;

each D moiety is independently a residue of an anticancer agent, an anticancer prodrug, a

detectable tag, or combinations thereof;

Z is covalently linked to $[D]_y$, wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

Y_1, Y_2, Y_3 and Y_4 are each independently O, S, or NR_{12};

R_{11} is a mono- or divalent polymer residue;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkylcarbonyls;

Ar is a moiety which when included in Formula (I) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

(m), (r), (s), (t), and (u) are independently zero or one; and

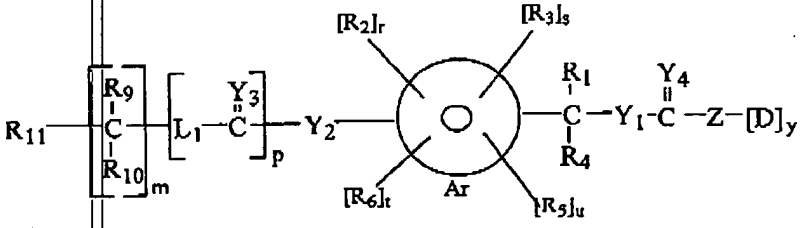
(p) is zero or a positive integer; and (y) is 1 or 2;

~~wherein Z[D]$_y$ is capable of crossing the membrane of the and is capable of being hydrolyzed therein to release D.~~

Please amend claim 37 as follows:

37. (Amended) A compound of Formula I:

(I)



wherein:

~~L_1 C(=Y_3) comprises an amino acid residue, wherein~~ L_1 is a bifunctional linking moiety ~~and Y_3 is as defined below~~;

D is a moiety that is a leaving group, or a residue of a compound to be delivered into a cell;

Z is covalently linked to $[D]_y$, wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

Y_1, Y_2, Y_3 and Y_4 are each independently O, S, or NR_{12};

R_{11} is a mono- or divalent polymer residue;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkylcarbonyls;

Ar is a moiety which when included in Formula (I) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

(m), (r), (s), (t), and (u) are independently zero or one; and

(p) is zero or a positive integer; and (y) is 1 or 2;

~~wherein $Z[D]_y$ is capable of crossing the membrane of the and is capable of being hydrolyzed therein to release D.~~

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July 24, 2003
MUSERLIAN, LUCAS & MERCANTI, LLP

BY: _____
Michael N. Mercanti